Complete Summary

GUIDELINE TITLE

Drotrecogin alfa (activated protein C) use for adult patients with sepsis.

BIBLIOGRAPHIC SOURCE(S)

Fishman N, Fuchs B, Manaker S, Hanson W, Sarani B, Taichman D, Christie J, Kahn J, Kinniry P, Umscheid CA, Williams K. Drotrecogin alfa (activated protein C) use for adult patients with sepsis: recommendation statement. Philadelphia (PA): University of Pennsylvania Health System; 2007 Jan 30. 17 p. [13 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Sepsis

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Risk Assessment
Treatment

CLINICAL SPECIALTY

Critical Care
Infectious Diseases
Internal Medicine

INTENDED USERS

Hospitals
Physicians

GUIDELINE OBJECTIVE(S)

To re-evaluate the formulary status and policy for use of Activated protein C within the University of Pennsylvania Health System

TARGET POPULATION

Adult patients with sepsis in the University of Pennsylvania Health System

INTERVENTIONS AND PRACTICES CONSIDERED

Activated protein C (drotrecogin alfa) following assessment of risk of death

MAJOR OUTCOMES CONSIDERED

- 28 day mortality
- Serious bleeding events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Patient Registry Data
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Task Force agreed to perform a systematic review of the association of Activated protein C with the outcomes of mortality at 28 days and serious bleeding events. Center representatives performed a systematic review of MEDLINE and the Cochrane library for controlled clinical trials that evaluated the use of Activated protein C in an adult intensive care unit (ICU) population. MEDLINE was searched using the terms "sepsis", "sepsis syndrome", "septic shock", "septicemia", AND "drotrecogin", "activated protein C", "zovant", "activated protein c", or "recombinant protein". The results were further limited to humans, English language, and clinical trial and 30 references were obtained. Scanning of titles and abstracts led to the selection of 12 separate publications for data abstraction. Further data was also obtained from the initial U.S. Food and Drug Administration (FDA) review of Activated protein C on the FDA website and clinical trials.gov.

Following the review of the published data, the Center for Evidence-based Practice (CEP) task force invited physician representatives from the manufacturer of Activated protein C (Eli Lilly) to present to the group. These presentations occurred on November 16, 2006. The task force also reviewed the indications and outcomes of all patients who have received Activated protein C at the Hospital of the University of Pennsylvania since FDA approval.

NUMBER OF SOURCE DOCUMENTS

12 publications were selected for data abstraction.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

GRADE* rating scheme for quality of evidence:

Type of evidence
Randomized trial = high
Quasi-randomized trial = moderate
Observational study = low
Any other evidence = very low

Decrease grade if:

Serious (-1) or very serious (-2) limitation to study quality
Important inconsistency (-1)
Some (-1) or major (-2) uncertainty about directness
Sparse data (-1)
High probability of reporting bias (-1)

Increase grade if:

Strong evidence of association-significant relative risk of >2 (
Very strong evidence of association-significant relative risk of >5 (
Evidence of a dose response gradient (+1)
All plausible confounders would have reduced the effect (+1)

*GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The results for the outcomes of 28 day mortality and serious bleeding events were abstracted from the relevant studies and evidence tables were developed (see attachment to the original guideline document). These tables presented the outcomes for the total trial populations as well as the subgroups of APACHE (Acute Physiology and Chronic Health Evaluation) II score <25, APACHE II >25, single organ dysfunction, and multiple organ dysfunction ($\geq$2 organs). Meta-analyses were performed where appropriate. Findings were reviewed with members of the task force.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Evidence tables were reviewed with the members of the task force and the quality of evidence for each outcome was graded by consensus using the GRADE approach. Next, the benefits and risks of the use of Activated protein C in the relevant populations were weighed, and recommendations for use were developed. The strength of each recommendation was graded by consensus using the GRADE approach.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

GRADE* rating scheme for strength of recommendation:

- Strong conclusion: Based on the balance of benefits and harms, the evidence clearly favors using or not using the intervention.
- Weak conclusion: Based on the balance of benefits and harms, the evidence probably favors using or not using the intervention, or is equivocal.

*GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was developed through methods of consensus development and was approved by the Chief Medical Officer (CMO) of each hospital in the University of Pennsylvania Health System (UPHS) for dissemination and implementation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The rating schemes for the quality of the evidence (very low, low, moderate, high) and the strength of the recommendations (weak, strong) are defined at the end of the "Major Recommendations" field.

1. The task force supports the targeted use of Activated protein C in adult patients with sepsis who are judged to be at high risk of death and opposes its use in patients who are not at high risk of death. *(Strong Recommendation, Moderate Quality Evidence)*
2. An assessment of patients' risk of death should consider, but should not be limited to, the patients' APACHE (Acute Physiology and Chronic Health Evaluation) scores or number of dysfunctional organs. *(Strong Recommendation, Low Quality Evidence)*
    - Patients who do not have either multi-organ dysfunction or APACHE scores >25 should not receive Activated protein C as there is certain harm and unclear benefit in this population.
    - Patients who are judged to be at "low risk of death" by an experienced clinician should not receive Activated protein C.
    - In patients who do have multi-organ dysfunction or an APACHE score >25, Activated protein C can then be used if an experienced clinician additionally judges the patient to be at "high risk of death".

3. The task force supports the current policy at the Hospital of the University of Pennsylvania (HUP) that the treating physician, the Pharmacy and Therapeutics (P&T) physician representative, and the intensive care unit (ICU) director must all agree that a patient is at a "high risk of death" before Activated protein C is administered. The task force encourages all hospitals in the health system to adopt a policy that incorporates a similar multi-tiered approval process involving at least the ICU director and the treating physician. *(Strong Recommendation, Very Low Quality Evidence)*

Definitions:

GRADE* rating scheme for quality of evidence:

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Any other evidence = very low

Decrease grade if:

Serious (-1) or very serious (-2) limitation to study quality
Important inconsistency (-1)
Some (-1) or major (-2) uncertainty about directness
Sparse data (-1)
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Increase grade if:

Strong evidence of association-significant relative risk of >2 (
Very strong evidence of association-significant relative risk of >5 (
Evidence of a dose response gradient (+1)
All plausible confounders would have reduced the effect (+1)

GRADE* rating scheme for strength of recommendation:

- Strong conclusion: Based on the balance of benefits and harms, the evidence clearly favors using or not using the intervention.
- Weak conclusion: Based on the balance of benefits and harms, the evidence probably favors using or not using the intervention, or is equivocal.

*GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting each recommendation was not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

If used appropriately in patients at "high risk of death," activated protein C could result in a significant reduction in mortality.

POTENTIAL HARMS

A meta-analytic estimate of the three randomized trials of Activated protein C versus placebo suggest that Activated protein C approximately doubles the risk of serious bleeding events with a statistically significant absolute risk increase of approximately 1 to 2%.

CONTRAINDICATIONS

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See the "Major Recommendations" field for details about patients who should not receive Activated protein C.

QUALIFYING STATEMENTS

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These recommendations are based on a systematic review of the evidence and an assessment of the important trade-offs between the potential benefits and harms of Activated protein C use. It is a guideline that should inform but not replace expert clinical judgment.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Fishman N, Fuchs B, Manaker S, Hanson W, Sarani B, Taichman D, Christie J, Kahn J, Kinniry P, Umscheid CA, Williams K. Drotrecogin alfa (activated protein C) use for adult patients with sepsis: recommendation statement. Philadelphia (PA): University of Pennsylvania Health System; 2007 Jan 30. 17 p. [13 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2007 Jan 30

GUIDELINE DEVELOPER(S)

University of Pennsylvania Health System - Academic Institution

SOURCE(S) OF FUNDING

The University of Pennsylvania Health System Office of the Chief Medical Officer provided support for the development of this guideline.

GUIDELINE COMMITTEE

University of Pennsylvania Health System (UPHS) Activated Protein C Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Neil Fishman MD; Barry Fuchs MD; Scott Manaker MD; William Hanson MD; Babak Sarani MD; Darren Taichman MD; Jason Christie MD, MSCE; Jeremy Kahn MD MSc; Paul Kinniry MD; Craig A. Umscheid MD, MSCE; and Kendal Williams MD, MPH

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

JC reports having received unrestricted grant support from Eli Lilly, the manufacturer of aprotinin, and abstained from voting on the final guideline. No other potential conflict of interest relevant to this guideline was reported.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) by request. Please contact Katie.thomas@uphs.upenn.edu.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on October 3, 2007. The information was verified by the guideline developer on October 31, 2007.

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